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| (21) International Application Number: PCT/GB95/02498 (22) International Filing Date: 20 October 1995 (20.10.95) (30) Priority Data: 9421394.9 24 October 1994 (24.10.94) GB (71) Applicant (for all designated States except US): OXFORD BIOSCIENCES LIMITED [GB/GB]; The Magdalen Centre, The Oxford Science Park, Oxford OX4 4GA (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): BELLHOUSE, Brian, John [GB/GB]; The Lodge, North Street, Islip, Oxfordshire OX5 2SQ (GB). DRAYSON, Paul, Rudd [GB/GB]; Bridge Cottage, Old Minster Lovell, Oxfordshire OX8 5RN-(GB). GREENFORD, John, Christopher [GB/GB]; 11 Park Crescent, Abingdon, Oxfordshire OX14 1DF (GB). SARPHE, David, Francis [GB/GB]; 78 Hailey Road, Witney, Oxfordshire OX8 5SH (GB). (74) Agent: GILL JENNINGS & EVERY; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB). | | (81) Designated States: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). ARIPO patent (KE, MW, SD, SZ, UG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> |
| (54) Title: PARTICLE DELIVERY | | |
| (57) Abstract | | |
| <p>A needleless syringe comprising an elongate nozzle (5) at the upstream end of which is an open ended capsule chamber (19) in axial alignment with the nozzle and arranged, in use, to contain and intimately enclose a soft-walled capsule (19A) containing particles of a therapeutic agent, means (21) at the upstream end of the capsule chamber for piercing the upstream end of a capsule in the chamber, and energizing means (12) for applying through the open upstream end of the capsule chamber, after the capsule has been pierced, a gaseous pressure sufficient to force the particles out through the downstream end of the capsule and the open downstream end of the capsule chamber and thus to create through the nozzle (5) a supersonic gas flow in which the particles are entrained.</p> | | |
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PARTICLE DELIVERY

In our earlier international patent application No. WO 94/24263, we disclose a non-invasive drug delivery system involving the use of a needleless syringe which fires light drug-containing particles in controlled doses into the intact skin or delivers genetic material into living cells. The syringe described in the earlier application is constructed as an elongate tubular nozzle, a rupturable membrane initially closing the passage through the nozzle adjacent to the upstream end of the nozzle, particles of a therapeutic agent, particularly a powdered therapeutic agent, located adjacent to the membrane, and energizing means for applying to the upstream side of the membrane a gaseous pressure sufficient to burst the membrane and produce through the nozzle a supersonic gas flow in which the particles are entrained.

By appropriate selection of the geometry and Mach number for the nozzle, which preferably has a convergent upstream portion, leading through a throat to a cylindrical or, preferably, divergent downstream portion, it has been possible to provide a pseudo-steady state, supersonic two phase flow through the nozzle, in which the particles move with a velocity close to that of the propelling gas in which they are entrained. Consequently, a large proportion of the particles reach the target under quasi-steady flow conditions and only a small proportion are delivered in transient flow and carried on the contact surface. This leads to considerable benefit both in control and in increased skin or other target penetration and is surprising in such a transient phenomenon.

In the earlier application it was proposed that the particles be contained within a capsule consisting of a pair of the rupturable membranes arranged face to face transversely to the axis of the nozzle and sealed together around their edges by means of an intervening ring provided with sealing means for sealing the periphery of the capsule

to a tubular body of the syringe. A capsule of this construction is quite complex for a disposable part and may provide an uncertain dose of the therapeutic agent if a proportion of the particles become entrapped behind the edges of the downstream membrane upon delivery.

In accordance with the present invention, a needleless syringe comprises an elongate nozzle at the upstream end of which is an open ended capsule chamber in axial alignment with the nozzle and arranged, in use, to contain and intimately enclose a soft-walled capsule containing particles of a therapeutic agent, means at the upstream end of the capsule chamber for piercing the upstream end of a capsule in the chamber, and energizing means for applying through the open upstream end of the capsule chamber, after the capsule has been pierced, a gaseous pressure sufficient to force the particles out through the downstream end of the capsule and the open downstream end of the capsule chamber and thus to create through the nozzle a supersonic gas flow in which the particles are entrained.

The capsule for use in the new syringe may have a gelatine wall and be substantially cylindrical with domed ends, such as are commonly used in, for example, inhalers used by asthmatics. By using tried and tested technology for creating and filling the capsules, the development and launching of the syringe can be carried out speedily and at low cost.

The capsule chamber for intimately enclosing the capsule may be formed within two separable wall parts which are divided transversely to the axis of the nozzle. In use the two parts will be separated to insert a capsule and then drawn axially together around the capsule. The two wall parts of the chamber may be held together by entrapment between two parts of the syringe body, which are, for example, interconnected by a screw-threaded, bayonet or other releasable connection.

The means for piercing the upstream end of the capsule may be a tubular or other cutter projecting into the

capsule chamber from the upstream end of the chamber wall, and being arranged to pierce the upstream end of the capsule as the two parts of the chamber wall are drawn together. Alternatively the upstream end of the capsule
5 may be pierced by a skewer which extends into the chamber through the opening at its upstream end.

In order to enable the particles to be readily forced out through the downstream end of the capsule and through the open downstream end of the capsule chamber and hence
10 into the nozzle, the downstream end of the capsule may be pierced similarly to the upstream end. Alternatively, the downstream end of the capsule may be moulded or otherwise formed with a weakened portion, such as in a cruciform shape, so that the downstream end of the capsule readily
15 ruptures when the necessary gas pressure is applied to initiate the flow through the capsule and along the nozzle.

In order to increase the pressure build-up prior to the supersonic flow, and hence to increase the supersonic velocity, the interconnection between the capsule chamber and the nozzle may be closed initially by a rupturable
20 membrane of, for example, Mylar, extending across the axis. In a similar position, a fine mesh may be provided in order to retain any parts of the capsule wall which might otherwise be entrained in the gas flow through the nozzle.

The energizing means may take any of the forms referred to in our earlier application, for example a pressure chamber upstream of the capsule chamber and means
25 for the controlled build-up of gaseous pressure in the pressure chamber, or a pressure chamber upstream of the capsule chamber containing a reservoir of compressed gas, together with means for releasing the pressure from the
30 reservoir for drug delivery.

In other respects, for example in the use of a spacer/silencer at the downstream end of the nozzle, in the
35 nozzle geometry, and in the type of particle which may be delivered, and in the type and pressure of gas to be used, reference is made to the earlier application.

An example of a syringe constructed in accordance with the present invention is illustrated in the accompanying drawings, in which:

- Fig. 1 is an axial section;
5 Fig. 2 is an elevation;
Fig. 3 is a side elevation of a capsule; and,
Fig. 4 corresponds to part of Fig. 1 but of a modified syringe.

The illustrated syringe has a barrel portion formed by
10 rigidly interconnected parts 3 and 4 and a tubular nozzle
5, which has a convergent/divergent passage 5A, and to
which the barrel part 4 is interconnected by screw-threads
6. The lower end of the nozzle 5 is provided with a shroud
7 and silencer 8. The barrel part 4 has a passageway 9
15 interconnecting the interior of the barrel part 3 with a
compartment 10 via a ring of ducts 11. The barrel part 3
is arranged to receive through its open upper end a bulb 12
containing pressurized gas and having a neck 13 which is
insertable downwards into the passage 9, to which it is
20 sealed by a O-ring 14. The outlet from the bulb 12 through
the neck 13 is closed by a spring-loaded ball valve 15. A
spigot 16 which is fixed in the barrel part 4 and extends
into the neck 13 of the bulb, is arranged to open the ball
valve against spring action when the bulb is pushed further
25 than the illustrated position down into the barrel part 3,
e.g. by the thumb of a person's hand holding the barrel in
its palm.

Mounted between the barrel part 4 and the nozzle 5 is
a capsule holder formed by two hollow parts 17 and 18.
30 When brought together as illustrated, these parts define an
internal capsule chamber 19 of substantially cylindrical
shape with domed ends, the chamber being arranged to
contain a soft-walled, powdered drug containing capsule 19A
of complementary shape. The parts 17 and 18 are held
35 together between the nozzle 5 and an inwardly projecting
rib 20 on the upper barrel 4 when the barrel part 4 is
screwed on to the nozzle. The remote ends of the parts 17

and 18 are both provided with fixed tubular cutters 21, 21A which are arranged to pierce the ends of the capsule when, with the capsule between the parts 17 and 18, the parts 17 and 18 are drawn together by screwing up of the barrel part 4 on to the nozzle 5. In this assembled configuration, depression of the end of the bulb down into the barrel part 3 causes the spigot 16 to open the valve 15 and to release the gas pressure within the bulb, which then flows through ducts 11, compartment 10, and into the upper end of the capsule chamber 19. When sufficient pressure has built up, a supersonic flow is created through the interior passage in the nozzle 5, with the particles being flushed out of the capsule and entrained in the gas flow, and hence carried out through the shroud into a patient's skin.

A Mylar membrane 22, rupturable to release the gas flow, and/or a screen, may be trapped between the bottom of the chamber part 18 and the upper end of the nozzle 5 as shown in Fig. 4, for the previously explained reasons. The membrane 22 is formed at its edges with a lip 22A, which is received in an annular groove in the top face of the nozzle 5, to seal the parts 5 and 18 together. The lip 22A thus replaces the O-ring 22B shown in Fig. 1.

After discharge of the syringe, the barrel part 4 will be unscrewed from the nozzle 5 to enable removal and disposal of the remnants of the capsule, and also of the Mylar membrane if used. The bulb 12 will also be withdrawn for disposal. In most cases the remaining parts of the syringe may be reused with new disposable parts.

Instead of the lower cutter 21, the lower end of the capsule 19A may be weakened, e.g. by cruciform lines of weakness 23, as shown in Fig. 3. The diaphragm 22 should not then be needed.

The shroud and silencer 7,8 are similar to those described in the earlier application to the extent that the shroud is a tubular part extending beyond the end of the nozzle 5, and the silencer includes an annular passage 8A between an upper portion of the shroud 7 and a lower

portion of the nozzle 5, the passage leading from within the shroud 7 to a ring of vents 8B opening out through the upper part of the shroud to the atmosphere. The interior of the passageway is irregular in the sense that both the inner wall of the shroud and the outer wall of the nozzle are stepped as shown at 8C thereby providing surfaces for the flow resulting from reflection of the shockwave at the patient's skin, to make multiple reflections, and thus dissipating the energy and noise. There may be a plurality of the steps 8C at axially spaced positions along the shroud and nozzle, with at least some adjacent pairs facing one another diagonally across the passage 8A, in a similar way to that in which the steps 8C face one another.

Alternatively, instead of being provided with the steps 8C, the passage may be filled with a helical vane, which causes multiple reflections from the adjacent axially facing turns of the vane as the gas flow passes generally helically along the passage. Such helical vane may be formed by moulding a helical flight on the outside of the nozzle and a complementary helical flight on the inside of the shroud, the two being brought into angular alignment when the shroud is fitted to the nozzle.

These constructions of silencer form independent features of the invention and may be used with any needleless syringe of the kind in which particles are entrained in a supersonic gas flow through a nozzle to the downstream end of which a shroud and silencer is fitted.

Typically, the gas provided in the chamber 14 may be helium at a pressure of the order of 40 to 80 bar. The nozzle may be of convergent/divergent, or convergent/cylindrical form with a length of between 50 and 100, preferably 60mm, and a throat diameter of between 1 and 10, preferably between 1.5 and 5mm. With appropriate gas pressure, particles having a diameter of 10-40 μ m will be accelerated through the nozzle to velocities of between Mach 1 and 3.

CLAIMS

1. A needleless syringe comprising an elongate nozzle (5) at the upstream end of which is an open ended capsule chamber (19) in axial alignment with the nozzle and arranged, in use, to contain and intimately enclose a soft-walled capsule (19A) containing particles of a therapeutic agent, means (21) at the upstream end of the capsule chamber for piercing the upstream end of a capsule in the chamber, and energizing means (12) for applying through the open upstream end of the capsule chamber, after the capsule has been pierced, a gaseous pressure sufficient to force the particles out through the downstream end of the capsule and the open downstream end of the capsule chamber and thus to create through the nozzle (5) a supersonic gas flow in which the particles are entrained.

2. A syringe according to claim 1, containing a capsule (19A) have a gelatine wall and being substantially cylindrical with domed ends.

3. A syringe according to claim 1 or claim 2, in which the capsule chamber (19) is formed within two separable wall parts (17,18) which are divided transversely to the axis of the nozzle.

4. A syringe according to claim 3, in which the two wall parts (17,18) of the chamber (19) are held together by entrapment between two parts (4,5) of the syringe which are interconnected by a releasable connection (6).

5. A syringe according to any one of the preceding claims, in which the means for piercing the upstream end of the capsule is a cutter (21) projecting into the capsule chamber (19) from the upstream end of the chamber.

6. A syringe according to claim 5 when dependent upon claim 3 or claim 4, in which the two wall parts (17,18) are arranged to be drawn axially together around the capsule, the cutter (21) being arranged to pierce the upstream end
5 of the capsule as the two wall parts are drawn together.

7. A syringe according to any one of the preceding claims, further comprising means (21A) at the downstream end of the capsule chamber (19) for piercing the downstream
10 end of a capsule (19A) in the chamber.

8. A syringe according to any one of claims 3 to 6 when dependent upon claim 2, in which the capsule (19A) is formed with a weakened portion (23) so that the downstream
15 end of the capsule readily ruptures when necessary gas pressure is applied to initiate the flow through the capsule and along the nozzle (5).

9. A syringe according to any one of claim 1 to 7, in
20 which the interconnection between the capsule chamber (19) and the nozzle (5) is additionally closed by a rupturable membrane extending across the axis of the nozzle.

10. A capsule for use in a syringe according to any one of
25 the preceding claims, the capsule (19A) having a gelatine wall, being substantially cylindrical with domed ends, and containing particles of a powdered drug.

11. A capsule according to claim 10, which is formed with
30 a weakened, readily rupturable portion at one end.

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Fig.1.

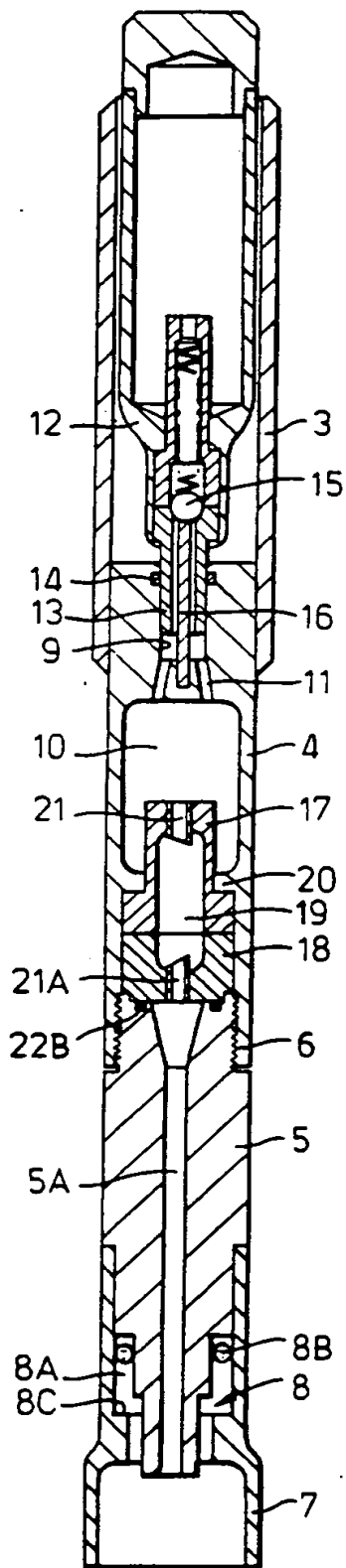


Fig.2.

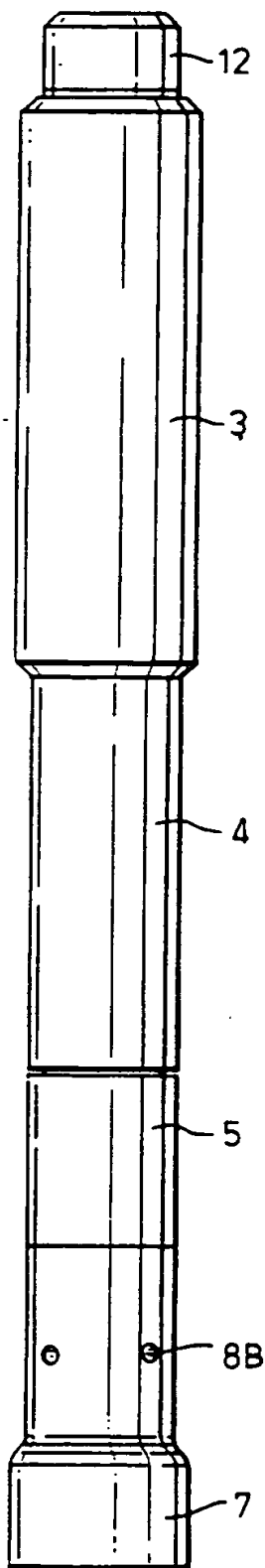


Fig.3.

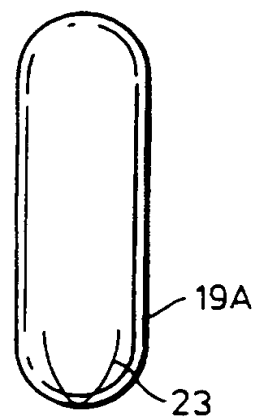
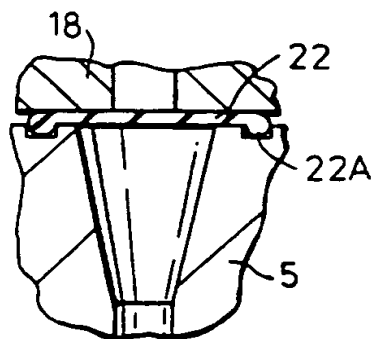


Fig.4.



INTERNATIONAL SEARCH REPORT

 International Application No
 PCT/GB 95/02498

 A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 A61M5/30 C12M3/00

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B. FIELDS SEARCHED

 Minimum documentation searched (classification system followed by classification symbols)
 IPC 6 A61M C12M

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Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|----------------------------------------------------------------------------------------------------------------|-----------------------|
| X,P | WO,A,95 19799 (AGRACETUS INC.) 27 July 1995 see page 5, line 2 - page 7, line 14 see figures 1,2 | 1 |
| A | US,A,3 853 125 (CLARK ET AL.) 10 December 1974 see column 2, line 41 - column 4, line 29 see figures 1,2 | 1 |
| A | US,A,3 949 751 (BIRCH ET AL.) 13 April 1976 see column 2, line 20 - column 3, line 47 see figures 1,2 | 1-3 |
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|----------|----------------------------------------------------------------------------------------------------------------------------|-----------------------|
| A | EP,A,0 387 222 (AKTIEBOLAGET DRACO) 12 September 1990 see column 7, line 42 -- line 43 see figure 8 | 2 |
| A | --- US,A,3 906 950 (COCOZZA) 23 September 1975 see column 2, line 43 - column 4, line 64 see figures 3,4 ----- | 3-7 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 95/02498

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|-------------------------------------------|---------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|
| WO-A-9519799 | 27-07-95 | AU-B- 1729595 CA-A- 2158733 EP-A- 0690732 | 08-08-95 27-07-95 10-01-96 |
| US-A-3853125 | 10-12-74 | SE-B- 394294 US-A- 3948266 | 20-06-77 06-04-76 |
| US-A-3949751 | 13-04-76 | GB-A- 1338254 AT-A,B 316732 BE-A- 764567 CA-A- 933829 CH-A- 538284 DE-A- 2114038 FR-A- 2085062 NL-A- 7103939 SE-B- 382914 SE-A- 7103839 | 21-11-73 15-06-74 20-09-71 18-09-73 15-08-73 18-11-71 17-12-71 28-09-71 23-02-76 |
| US-A-3998226 | 21-12-76 | GB-A- 1505608 JP-C- 912368 JP-A- 52039990 JP-B- 52040795 | 30-03-78 21-07-78 28-03-77 14-10-77 |
| EP-A-0387222 | 12-09-90 | SE-B- 466684 AU-B- 613264 AU-B- 5271090 CA-A- 2028830 DE-T- 69002353 JP-T- 3504457 NO-B- 175289 SE-A- 8900793 WO-A- 9010470 US-A- 5331953 | 23-03-92 25-07-91 09-10-90 08-09-90 02-12-93 03-10-91 20-06-94 08-09-90 20-09-90 26-07-94 |
| US-A-3906950 | 23-09-75 | BE-A- 813143 CH-A- 569486 DE-A- 2415961 FR-A,B 2224175 GB-A- 1436813 JP-A- 50048782 | 31-07-74 28-11-75 17-10-74 31-10-74 26-05-76 01-05-75 |